ISIS-2508

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Cook

Serial No.: **08/877,317** Group Art Unit: **1633**

Filed: **June 17, 1997** Examiner: **J. Martinell**

For: **PNA-DNA-PNA CHIMERIC MACROMOLECULES**

I, Gregory L. Hillyer, Registration No. 44,154 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On September 14, 2000

Gregory L. Hillyer Reg. No. 44,154

BOX AF
Assistant Commissioner of Patents
Washington, D.C. 20231

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 1.192

Applicants appeal the rejection of claims 13-16, 19, 20, and 24-26 under 35 U.S.C. §112, first paragraph, set forth in the Final Official Action mailed February 16, 2000 in connection with the above-identified patent application. An Amendment under 37 C.F.R. 1.116 was filed on May 5, 2000. An Advisory Action dated June 5, 2000 reaffirmed the rejections in the Final Official Action. A Notice of Appeal with appropriate fees was filed on July 14, 2000.

I. Real Party in Interest

The real party in interest in the above-identified patent application is Isis Pharmaceuticals, Inc., which is the assignee of inventor Phillip Dan Cook.

II. Related Appeals and Interferences

No appeals or interferences related to the above-identified patent application are believed to be pending.

III. Status of Claims

The present application was filed with original claims 1-23. Claims 13-16, 19, 20, and 24-26 are on appeal; they appear in the Appendix to this Brief.

IV. Status of Amendments

No amendment has been filed subsequent to the Examiner's final rejection as set forth in the Final Action mailed February 16, 2000.

V. Summary of the Invention

The present invention relates, *inter alia*, to Applicants' recognition that chimeric molecules having a PNA-DNA-PNA structure and a base sequence that is hybridizable to a RNA target molecule can bind to that target RNA molecule and elicit a RNase H-mediated strand cleavage of the target molecule.

The methods of the present invention involve modulation of the activity of a target RNA by providing chimeric macromolecules that hybridize with the target. It is well-known that most of the bodily states in mammals including most disease states, are effected by proteins. Such proteins, either acting directly or through their enzymatic functions, contribute in major proportion to many diseases in animals and man. Classical therapeutics has generally focused upon interactions with such proteins in an effort to moderate their disease causing or disease potentiating functions,

or by moderating the actual production of such proteins by interactions with messenger RNA (mRNA) or other intracellular RNA's that direct protein synthesis. It is generally the object of such therapeutic approaches to interfere with or otherwise modulate gene expression leading to undesired protein formation.

Hybridization is the sequence specific hydrogen bonding via Watson-Crick base pairs of the heterocyclic bases of oligonucleotides to RNA or DNA. Such base pairs are said to be complementary to one another. Antisense methodology is the complementary hybridization of relatively short oligonucleotides to single-stranded RNA or single-stranded DNA such that the normal, essential functions of these intracellular nucleic acids are disrupted.

Although it has been recognized that cleavage of a target RNA strand using an antisense oligonucleotide and RNase H would be useful, the susceptibity of oligonucleotides to nuclease degradation and their ability to hybridize with the target RNA have presented problems. Accordingly, there has been a long-felt need for methods and materials that could both activate RNase H while concurrently maintaining or improving hybridization properties and providing nuclease resistance.

It has been discovered that certain macromolecules assembled from a plurality of peptide nucleic acid (PNA) subunits and a plurality of DNA subunits have increased nuclease resistance, increased binding affinity to complementary strands, and are substrates for RNase H. The peptide nucleic acid subunits and the 2'-deoxynucleotide subunits include nucleobases that are capable of specifically hybridizing with nucleobases on target RNA molecules. The peptide nucleic

acid portions of the macromolecules of the invention are believed to confer increased nuclease resistance and increased binding affinity to a complementary strand of nucleic acid. Applicant's claimed invention relates to the recognition that oligonucleotides such as those described in claims 13-16, 19, 20, and 24-26, possess these beneficial properties.

VI. Issue

The issue to be resolved in this appeal is whether or not the Examiner has demonstrated that those skilled in the art would be unable to practice the inventions recited in claims 13-16, 19, 20, and 24-26.

VII. Grouping of the Claims

Applicants believe that claims 13-16, 19, 20, and 24-26 stand or fall together.

VIII. Argument

The rejection of claims 13-16, 19, 20, and 24-26 under 35 U.S.C. § 112, first paragraph, is improper and should be reversed, as there is no reason of record to believe that those skilled in the art would not be able to practice the claimed inventions.

The first paragraph of § 112 requires that the disclosure of a patent application be such that persons skilled in the art, having read the patent application, would be able to practice the inventions described by the claims. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). There is no legal requirement that this be done in any particular manner. An enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology. *In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971).

When rejecting a claim under the enablement requirement of § 112, the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the Examiner must provide evidence or technical reasoning substantiating those doubts. *Id.*; and MPEP § 2164.04.

Significantly, the Examiner has failed to provide any factual evidence indicating a reason to doubt that Applicant's disclosure would enable those skilled in the art to practice the claimed methods. It has been undisputed throughout prosecution that those skilled in the art would be able to practice such methods and produce measurable results. Although the Office Action notes that Rojanasakul, *Advanced Drug Delivery Reviews*, 18, 115-131 (1996) ("the Rojanasakul reference") discloses certain problems that allegedly would be encountered in the therapeutic use of oligonucleotides, this disclosure is not believed to support rejection of the claims for alleged lack of enablement. There is absolutely no requirement in the patent laws that patentable inventions be problem-free, and the Examiner has failed to demonstrate that any of the "problems" disclosed by the Rojanasakul reference are so significant as to entirely impede practice of the claimed methods.

In fact, the Examiner has pointedly failed to address disclosure in the Rojanasakul reference suggesting that his alleged "problems" would not impede practice of the claimed methods.

In this regard, the Rojanasakul reference states that compounds such as those recited in the claims show great promise:

> [s]everal ON drugs have already demonstrated enough promise to justify clinical trials. They are being tested in patients suffering from leukemia, AIDS, and other diseases in which improved treatments are necessary. It is expected that in the future these ON drugs will be commonly used to treat those diseases for which no effective therapies yet exist.

See, the Rojanasakul reference at page 126. This passage serves as compelling evidence that the state of the art of oligonucleotide therapeutics, at the time the present application was filed, was such that an artisan could readily obtain at least some measurable test results once armed with the teachings of the present application. The Examiner is not permitted to simply ignore the above-quoted text; the Rojanasakul reference must be considered as a whole. *In re Keller*, 642 F.2d 413, 425 (C.C.P.A. 1981).

Not only does the mere existence of problems associated with the claimed inventions not negate their patentablility, but such problems are to be *expected*. It is well-established that pharmaceutical inventions usually require further research and development. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Were such inventions not patentable long before being optimized or ready for human use, the incentive to fully research and develop vital drugs and potential cures would be completely removed. *Id.* at 1567-68.

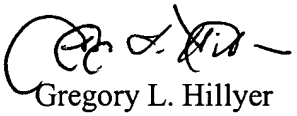
Thus, the Examiner's unsupported contentions as to alleged difficulties that those skilled in the art would encounter in practicing the claimed inventions simply do not constitute

evidence or technical reasoning of the sort required to substantiate allegations that there is a lack of enablement. To the extent that "problems" are identified in the Rojanasakul reference, such "problems" relate to optimizing the performance of a therapeutic product for clinical use. Since there is no requirement that an invention be optimized to be patentable, the disclosure of the Rojanasakul reference fails to support rejection of Applicant's claims, and hence, there is no basis for the rejection for lack of enablement.

IX. Conclusion

Applicants have provided ample guidance to teach those of skill in the art how to make and use the claimed invention. As the Examiner has failed to provide sound technical reasoning refuting such, the claims must be deemed enabled. Accordingly, the rejection of claims 21 and 28-32 under 35 U.S.C. § 112, first paragraph, is improper and should be reversed.

Respectfully submitted,



Gregory L. Hillyer
Registration No. 44,154

Date: September 14, 2000
WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100

ISIS-2508

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Cook

Serial No.: **08/877,317** Group Art Unit: **1633**

Filed: **June 29, 1995** Examiner: **J. Marinell**

For: **PNA-DNA-PNA CHIMERIC MACROMOLECULES**

Assistant Commissioner
for Patents
Washington, D.C. 20231

APPENDIX TO APPELLANT'S BRIEF

13. A method of treating an organism having a disease characterized by the undesired production of a protein, comprising contacting the organism with a macromolecule that has structure PNA-DNA-PNA and that includes a sequence of nucleobases capable of specifically hybridizing to a strand of nucleic acid coding for said protein, wherein:

said DNA includes at least one nucleotide having a 2'-deoxy-erythro-pentofuranosyl sugar moiety covalently bound to one of said nucleobases; and

each of said PNAs includes at least one peptide nucleic acid subunit having a covalently bound nucleobase.

14. A method of claim 13 wherein said nucleotide is a phosphorothioate nucleotide.

15. A method of claim 13 wherein said nucleotide is a phosphorodithioate nucleotide.

16. A method of claim 13 wherein said nucleotide is a phosphodiester nucleotide.

19. A method of enhancing polynucleotide hybridization in a organism, comprising contacting the organism with a macromolecule of the structure:

PNA-DNA-PNA

wherein:

said DNA comprises at least one 2'-deoxynucleotide;

each of said PNAs comprise at least one peptide nucleic acid subunit;

said macromolecule has a sequence of nucleobases capable of specifically hybridizing to a complementary strand of nucleic acid; and

some of said nucleobases are located on the PNA portions of said macromolecule and some of said nucleobases are located on the DNA portion of said macromolecule.

20. A method of treating an organism having a disease characterized by the undesired production of a protein, comprising contacting the organism with a compound of the structure:

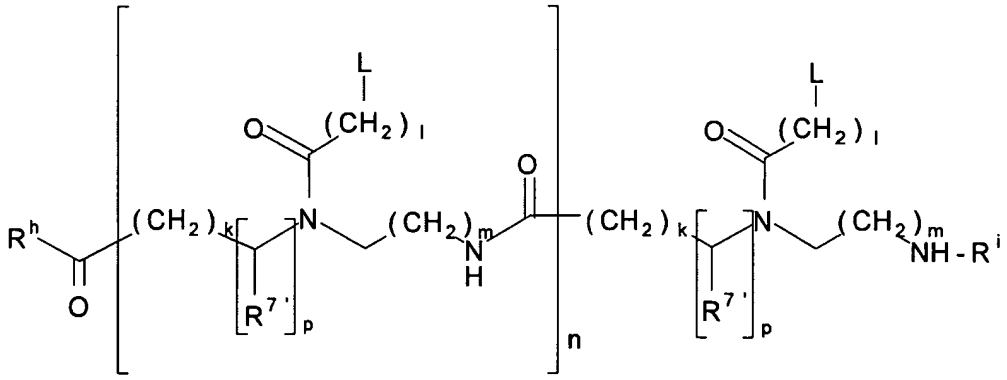
PNA-DNA-PNA

wherein:

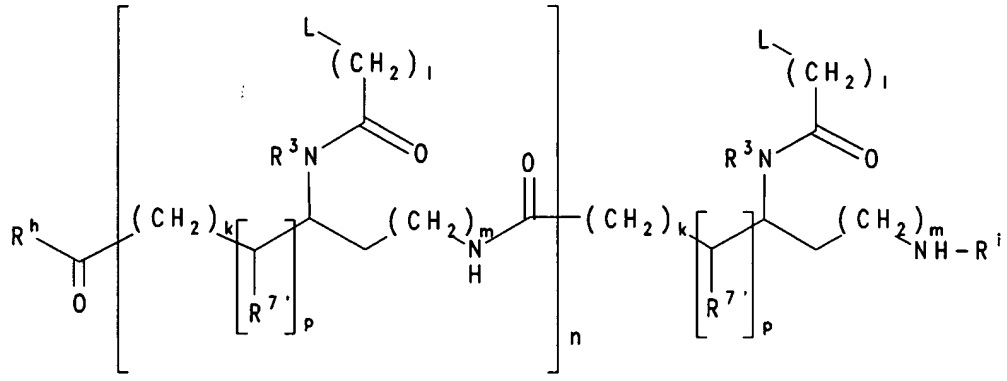
said DNA comprises at least one 2'-deoxynucleotide; and

each of said PNAs comprise at least one peptide nucleic acid subunit.

24. The method of claim 20 wherein said each of said PNAs comprises a compound of the formula IIIa, IIIb or IIIc:

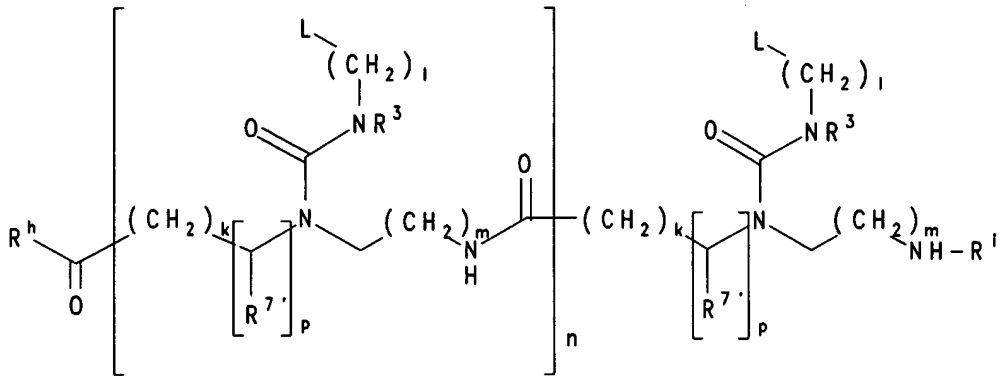


(IIIa)



(IIIb)

ISIS-2508



(IIIc)

wherein:

each L is independently selected from the group consisting of hydrogen, phenyl, heterocyclic moieties, naturally occurring nucleobases, and non-naturally occurring nucleobases;

each R^7 is independently selected from the group consisting of hydrogen and the side chains of naturally occurring alpha amino acids;

n is an integer from 1 to 60;

each of k, l, and m is independently zero or an integer from 1 to 5;

p is zero or 1;

R^h is OH, NH_2 or -NHLysNH$_2$; and

R^i is H or $COCH_3$.

25. The method of claim 24 where each of said PNAs comprise a compound having formula (IIIa)-(IIIc) wherein each L is independently selected from the group consisting of

the nucleobases thymine (T), adenine (A), cytosine (C), guanine (G) and uracil (U), k and m are zero or 1, and n is an integer from 1 to 30, in particular from 4 to 20.

26. The method of claim 25 wherein:

said DNA includes at least three of said 2'-deoxynucleotides linked together in a sequence:

each PNA includes at least two peptide nucleic acid subunits; and

said 2'-deoxynucleotides are joined via phosphodiester, phosphorothioate or phosphorodithioate linkages.